EXHIBIT 2 – PART B

EXHIBIT F

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4.0 Executive Summary

4.1 Background

Bare metal stents (BMS) became the preferred choice of treatment for percutaneous coronary interventions (PCI) after clinical trials indicated that stenting decreased reintervention rates compared with balloon angioplasty.[1,2,3] While BMS virtually eliminated many of the complications of abrupt artery closure and late vessel recoil associated with angioplasty, restenosis persisted, with rates as high as 20% to 40% in high-risk subgroups, necessitating a repeat procedure.[4,5,6] The principal cause of in-stent restenosis is neointimal hyperplasia resulting from migration and proliferation of smooth muscle cells and extracellular matrix production.[7]

Stents coated with anti-proliferative agents have been successful in addressing the problem of exuberant neointimal hyperplasia. Sometimes referred to as a "coated" or "medicated" stent, a drug-eluting stent (DES) is coated with a pharmacologic agent (drug) that is known to interfere with the process of restenosis (reducing neointimal growth). In multiple clinical trials, drug-eluting stents have been unequivocally shown to reduce reinterventions (angiographic restenosis) compared with bare metal stents (BMS), thereby reducing recurrent ischemia resulting in the need for repeat hospitalization and revascularization procedures.[8,9] Because of this, drug-eluting stents have become routine therapy in clinical practice, and a comparative standard for evaluation of novel anti-proliferative therapies and stent technologies.

The ideal drug eluting stent should provide for superior clinical efficacy compared to bare metal stents with equivalent safety as measured by cardiac death, myocardial infarction (MI) and stent thrombosis. Stent thrombosis associated with DES was the topic of the FDA Circulatory System Devices Panel meeting on December 7-8, 2006. FDA's purpose for this panel meeting was to provide a forum for the presentation of clinical data relevant to the issue of DES thrombosis and to address the appropriate duration of

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1 Al Suwaidi J, Berger PB, Holmes DR Jr. Coronary artery stents. JAMA. 2000;284:1828 –1836.
2 Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents: a hierarchical Bayesian meta-analysis. Ann Intern Med. 2003;138:777–786.
3 Nordmann AJ, Hengstler P, Leimenstoll BM, et al. Clinical outcomes of stents versus balloon angioplasty in non-acute coronary artery disease: a meta-analysis of randomized controlled trials. Eur Heart J. 2004;25:69–80.
4 Scheen AJ, Warzee F, Legrand VM. Drug-eluting stents: meta-analysis in diabetic patients. Eur Heart J. 2004;25:2167–2168.
5 Nikol S, Huehns TY, Hofling B. Molecular biology and post-angioplasty restenosis. Atherosclerosis. 1996;123:17–31.
6 Elezi S, Kastrati A, Neumann FJ, et al. Vessel size and long-term outcome after coronary stent placement. Circulation. 1998;98:1875–1880.
7 Mercado N, Boersma E, Wijns W,et al. Clinical and quantitative coronary angiographic predictors of coronary restenosis: a comparative analysis from the balloon-to-stent era. J Am Coll Cardiol. 2001;38:645–652.
8 Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
9 Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.

antiplatelet therapy in DES patients.[10] Among the conclusions of this meeting, the panel found that the concerns about thrombosis do not outweigh the benefits of DES compared to bare metal stents when DES are implanted within the limits of their approved indications for use. In addition, the panel found that larger and longer premarket clinical trials and longer follow-up for post-approval studies are needed.

The phenomenon of stent thrombosis is not new to percutaneous coronary intervention (PCI). Early stent thrombosis of freshly deployed stents has been a concern since their introduction to human coronary circulation in 1986.[11] The unacceptably high rates (up to 24%) of thrombotic events seen in early clinical experience were dramatically reduced through a combined anticoagulation and antiplatelet therapy after "optimal" stent expansion with routine high pressure post-dilatation. This appreciation for the multifactorial nature of stent thrombosis continued to reduce the incidence of stent thrombosis through attention to the procedure and patient education regarding appropriate use of dual anti platelet therapy. Despite dramatic reductions in stent thrombosis, it has not been eliminated; in this modern stent era, the incidence is reported to be roughly 1%.[11]

Although the majority of stent thrombosis events occur early (within the first 30 days post procedure), late stent thrombosis (> 30 days post-implant) out to one year is not an uncommon finding with BMS.[12,13,14,15] More recently, there has been a heightened awareness surrounding the incidence of stent thrombosis beyond one year (very late). Compared to BMS, the increased rate of very late stent thrombosis (> 12 months) with DES compared to BMS highlights a risk that may be unique to DES.[16,17,18,19] This observation indicating the potential association of the product (DES) with stent thrombosis is in addition to the previously identified risk factors – such as inadequate stent expansion and poor patient drug compliance. It is important that the development program for any new drug eluting stent fully characterize the product's safety profile in

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[10] Food and Drug Administration. Update to FDA Statement on Coronary Drug-Eluting Stents. January 4, 2007. http://www.fda.gov/cdrh/news/010407.html.

[11] Honda Y and Fitzgerald P. Stent thrombosis: An issue revisited in a changing world. Circulation 2003;108;2-5.

[12] Wenaweser P, Rey C, et al. Stent thrombosis following bare-metal stent implantation: success of emergency percutaneous coronary intervention and predictors of adverse outcome. Europena Heart Journal Journal 2005; 26: 1180-1187.

[13] Ramos AR, Morice M and Lefevre T. Late or very late stent thrombosis can also occur with bare metal stents. Catheterization and Cardiovascular Interventions 2007; 70: 229-232.

[14] BENESTENT: Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med. 1994;331: 489-495.

[15] STRESS: Fischman DL, Leon M, Baim DS, et al. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med. 1994;331: 496-501.

[16] Jensen LO, Maeng M, et al. Stent Thrombosis, Myocardial Infarction, and Death After Drug-Eluting and Bare-Metal Stent Coronary Interventions. JACC 2007; 50: 463-470.

[17] Kaul S, Shah P and Diamond GA. Current status and future directions in the controversy over stenting. JACC 2007; 50: 128-137.

[18] Jaffe R, and Strauss BH. Late and very late thrombosis of drug-eluting stents. JACC 2007; 50: 119-127.

[19] Mauri L, Hsieh W, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med. 2007; 356: 1020-1029.

addition to demonstrating its efficacy. In the following sections, the Endeavor Zotarolimus-Eluting CSS is described, followed by summaries of the drug development and relevant non-clinical and clinical testing programs for both the zotoralimus drug substance and the Endeavor product. The drug studies were performed according to standard ICH pharmacology guidelines and with consultation with FDA's Center for Drug Evaluation and Research. The Endeavor drug/stent/polymer combination product studies are described separately and were developed in consultation with the FDA's Center for Devices and Radiological Health, which is the designated lead center responsible for the review and approval of drug-eluting stent pre-market approval applications.

4.2 Product Description

The Endeavor Zotarolimus-Eluting Coronary Stent System is a device / drug combination product comprised of device components (the Driver™ Coronary Stent and the Micro-Driver™ Coronary Stents and the Endeavor delivery systems) and a drug component (a formulation of zotarolimus and Phosphorylcholine polymer coating).

The Endeavor product has four main components:

- Stent - the Endeavor stent component (bare metal substrate) is identical to the Driver and the Micro-Driver Coronary Stents
- Delivery Systems – the Endeavor OTW, RX and MX^2 delivery systems.
- Polymer - the Phosphorylcholine (PC) polymer is identical to that utilized in the Bio*divYsio*™ PC coated stent (P000011, approved September 29, 2000)
- Drug - the drug substance zotarolimus[20] (ABT-578), a member of the limus family of drugs commonly used for the indication.

The stent component of the Endeavor Zotarolimus-Eluting CSS is manufactured from a cobalt based alloy (MP35N) that has been successfully used in other implantable medical devices since 1985, including septal occluders, hip prostheses, aneurysm clips, pacing leads, vena cava filters, and bare metal coronary stents. The Endeavor stent is identical to the approved Driver (P030009, approved October 1, 2003) and the approved Micro-Driver (P030009/S002, approved April 21, 2006) coronary stents.

The Endeavor stent is mounted on one of three delivery systems. The three delivery systems offered with the Endeavor stent are the Over-The-Wire (OTW), Rapid Exchange (RX) and Multi Exchange II (MX^2) Delivery Systems. The delivery systems utilized for the Endeavor product are similar in materials, design and construction to the approved Driver OTW (P030009, approved October 1, 2003; Driver MX^2 P030009/S001, approved on August 4, 2004; Driver RX, P030009/S003, approved on December 22, 2005) and the approved Micro-Driver OTW and MX^2 (P030009/S002, approved on April 21, 2006) delivery systems.

The polymer coating on the Endeavor stent is the Phosphorylcholine (PC) polymer, which acts as a carrier for the drug zotarolimus. PC polymer was originally developed by Biocompatibles UK, Ltd. to increase the biocompatibility and hemocompatibility of

[20] The drug substance previously referred to as ABT-578 has been assigned the name Zotarolimus (Reference USAN [QQ-84] at www.ama-assn.org)

materials through biomembrane mimicry, as PC is the major lipid headgroup component found in the outer surface of biologic cell membranes. Reference Figure 4-1.

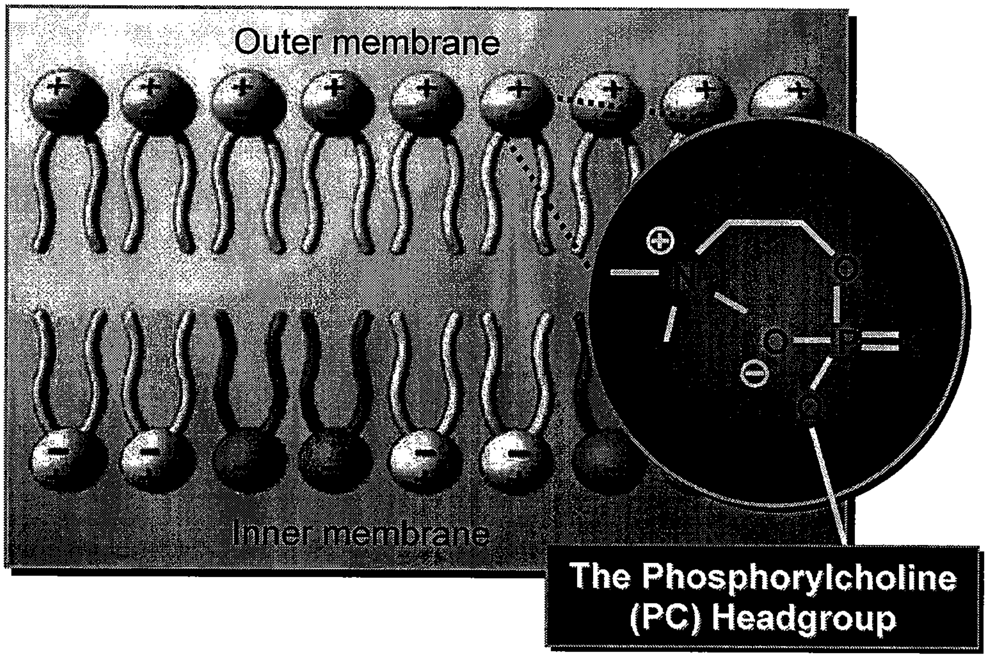


Figure 4-1: Graphical Depiction of Cell Membrane

PC polymer has been in use in Europe on coronary stents since 1997. The BiodivYsio PC coated stent was CE mark approved (Approval number: CE 02073) on September 4, 1998. PC-coated stents have also been in use since 2000 in the United States, marketed as the BiodivYsio™ as PC-Coated Stent and Delivery System (P000011, approved September 29, 2000). The BiodivYsio™ PC-coated stent has been successfully implanted worldwide in over 100,000 patients to date.[21,22,23,24,25,26,27] It has also been used in other medical implants where it has been shown to decrease thrombin formation on devices used for cardiac surgery [28] and to decrease platelet deposition when coated on

[21] Cumberland DC, et al. Biomimicry 1:PC. Seminars in Interventional Cardiology 1998 Sep-Dec; 3(3-4): 149-50.
[22] Kuiper KK, Robinson KA, Chronos NAF, Cui J, Palmer SJ, Nordrehaug JE. Phosphorylcholine-coated metallic stents in rabbit iliac and porcine coronary arteries. Scand Cardiovasc J 1998; 32(5): 261-268.
[23] Zheng H, Barragan P, Corcos T, Simeoni JB, Favereau X, Roquebert PO, et al. Clinical experience with a new biocompatible phosphorylcholine-coated coronary stent. J Invasive Cardiol; 1999 Oct; 11(10): 608-614.
[24] Whelan DM, van der Giessen WJ, Krabbendam SC, van Vliet EA, Verdouw PD, Serruys PW, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. Heart 2000 Mar; 83(3): 338-345.
[25] Boland JL, Corbeij HAM, van der Giessen W, Seabra-Gomes R, Suryapranata H, Wijns W, et al. Multicenter evaluation of the phosphorylcholine-coated biodivYsio stent in short de novo coronary lesions: The SOPHOS study. Int J Cardiovasc Intervent 2000 Dec; 3(4): 215-225.
[26] Atalar E, Haznedaroglu I, Aytemir K, Aksoyek S, Ovonc K, Oto A, et al. Effects of stent coating on platelets and endothelial cells after intracoronary stent implantation. Clin Cardiol 2001 Feb; 24(2): 159-164.
[27] Malik N, Gunn J, Shepherd L, Crossman D, Cumberland DC, Holt CM. Phosphorylcholine-coated stents in porcine coronary arteries: In-vivo assessment of biocompatibility. J Invasive Cardiol 2001 Mar; 13(3): 193-201.
[28] F. Pappalardo, P. D. Valle, G. Crescenzi, C. Corno, A. Franco, L. Torracca, O. Alfieri, L. Galli, A. Zangrillo, and A. D'Angelo Phosphorylcholine Coating May Limit Thrombin Formation During High-Risk Cardiac Surgery: A Randomized Controlled Trial Ann. Thorac. Surg., March 1, 2006; 81(3): 886 - 891.

arteriovenous (AV) grafts.[29] Clinical investigations and *in-vivo* animal studies have shown that the polymer reduces thrombus formation and does not elicit inflammatory effect.[30,31,32,33,34,35,36] Animal data have also demonstrated that the Endeavor Zotarolimus-Eluting CSS with PC polymer has a low inflammation score of 0.1 and 0.6 similar to that of the BMS at 28 and 90 days post implant.[37] In concert, the above referenced clinical and *in-vitro* information available on the PC polymer, combined with the studies performed on the Endeavor Zotarolimus-Eluting CSS demonstrate that the polymer is biocompatible.

The Endeavor drug component, zotarolimus, is a tetrazole–containing macrocyclic immunosuppressant. The coating present on the Endeavor Zotarolimus-Eluting CSS is comprised of a base coating layer consisting of 100% PC polymer, followed by a zotarolimus and PC polymer matrix layer. A 100% PC polymer overspray is applied once the stent is mounted on the balloon. Coating layer thickness is greater on the abluminal side of the stent. A representative schematic is shown in Figure 4-3 (not to scale).

[29] Chen C, Ofenloch JC, Yianni YP, Hanson SR, Lumsden AB. Phosphorylcholine coating of ePTFE reduces platelet deposition and neointimal hyperplasia in arteriovenous grafts. J Surg Res 1998; 77: 119–125.

[30] Cumberland DC, et al. Biomimicry 1:PC. Seminars in Interventional Cardiology 1998 Sep-Dec; 3(3-4): 149-50.

[31] Kuiper KK, Robinson KA, Chronos NAF, Cui J, Palmer SJ, Nordrehaug JE. Phosphorylcholine-coated metallic stents in rabbit iliac and porcine coronary arteries. Scand Cardiovasc J 1998; 32(5): 261-268.

[32] Zheng H, Barragan P, Corcos T, Simeoni JB, Favereau X, Roquebert PO, et al. Clinical experience with a new biocompatible phosphorylcholine-coated coronary stent. J Invasive Cardiol; 1999 Oct; 11(10): 608-614.

[33] Whelan DM, van der Giessen WJ, Krabbendam SC, van Vliet EA, Verdouw PD, Serruys PW, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. Heart 2000 Mar; 83(3): 338-345.

[34] Boland JL, Corbeij HAM, van der Giessen W, Seabra-Gomes R, Suryapranata H, Wijns W, et al. Multicenter evaluation of the phosphorylcholine-coated biodivYsio stent in short de novo coronary lesions: The SOPHOS study. Int J Cardiovasc Intervent 2000 Dec; 3(4): 215-225.

[35] Atalar E, Haznedaroglu I, Aytemir K, Aksoyek S, Ovonc K, Oto A, et al. Effects of stent coating on platelets and endothelial cells after intracoronary stent implantation. Clin Cardiol 2001 Feb; 24(2): 159-164.

[36] Malik N, Gunn J, Shepherd L, Crossman D, Cumberland DC, Holt CM. Phosphorylcholine-coated stents in porcine coronary arteries: In-vivo assessment of biocompatibility. J Invasive Cardiol 2001 Mar; 13(3): 193-201.

[37] Virmani, R. "Past Predictions, Current Perspectives, Future Forecasts of Drug-Eluting Stents: View of the Pathologist." Presented at the: *EuroPCR Conference*; official annual meeting of the European Association of Percutaneous Cardiovascular Interventions (2006)

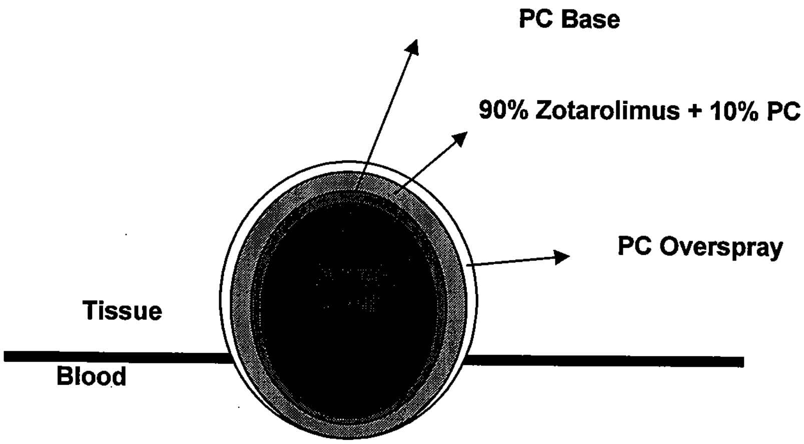


Figure 4-2: Cross Section of an Endeavor Stent Strut – a schematic (not to scale)

The relative thickness is such that the PC overspray is not a distinguishable layer. A scaled schematic of the various coating layers is provided in Figure 4-3.

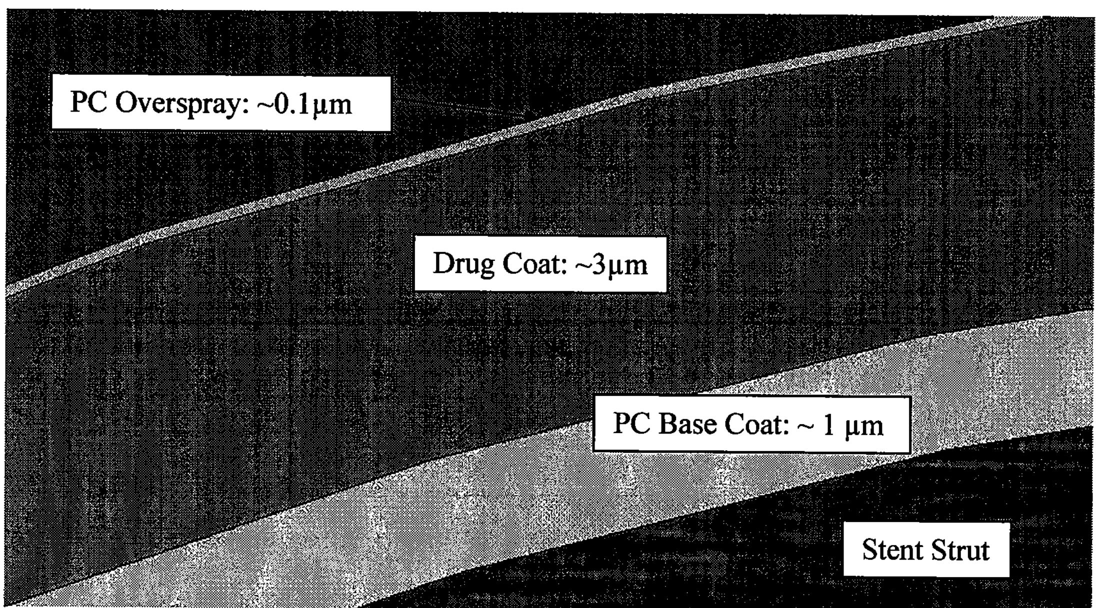


Figure 4-3: Schematic of Endeavor coatings, drawn to relative scale

The product matrix associated with this PMA application for the Endeavor Zotarolimus-Eluting OTW, RX and MX2 products is provided in Table 4-1, below:

Table 4-1: The Endeavor Product Size Matrix

Diameter (mm)	Stent Length (mm)							
	8	9	12	14	15	18	24	30
2.5	✓	N/A	✓	✓	N/A	✓	✓	✓
3.0	N/A	✓	✓	N/A	✓	✓	✓	✓
3.5	N/A	✓	✓	N/A	✓	✓	✓	✓

4.3 Drug Substance (Zotarolimus)

The drug substance, zotarolimus, is utilized on the Endeavor Zotarolimus-Eluting Coronary Stent System (CSS) at a dose of 10µg/mm of stent length. Zotarolimus (also referred to as ABT-578) is supplied to Medtronic Vascular through a licensing agreement with Abbott Laboratories and is manufactured by

Zotarolimus, which was originally developed in 1997 as an immunosuppressant to treat rheumatoid arthritis, is a semi-synthetic tetrazole-containing molecule of the limus family. In 1998, zotarolimus had been identified as a potent smooth muscle cell inhibitor and recognized its potential for use as an active ingredient on a drug eluting stent. By 2001, animal studies had been performed that showed potential for the anti-proliferative mechanism of zotarolimus to be used in coronary stent applications. On the basis of review of these studies, Medtronic Vascular licensed the use of zotarolimus from Abbott Laboratories in 2002 for use in Endeavor Zotarolimus-Eluting CSS and other development projects. There are currently no oral or intravenous formulations of zotarolimus available.

A detailed description of the drug substance zotarolimus and its physicochemical characteristics is provided in Drug Master File (DMF) #16960 (submitted to FDA on Nov 14, 2003 by Abbott Laboratories). A summary of those physicochemical characteristics important to use of the drug substance in Endeavor Zotarolimus-Eluting CSS is provided in the following pages.

The mechanism of action of zotarolimus is to bind to the intracellular protein, FKBP12, leading to the formation of a trimeric complex with mTOR (mammalian target of rapamycin). The protein kinase activity of mTOR is thus inhibited which results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control. The mechanism of action is graphically represented in Figure 4-4. *In vitro*, zotarolimus demonstrated binding affinity with FKBP-12 and potently inhibited growth factor-induced proliferation of human coronary artery smooth muscle cells.

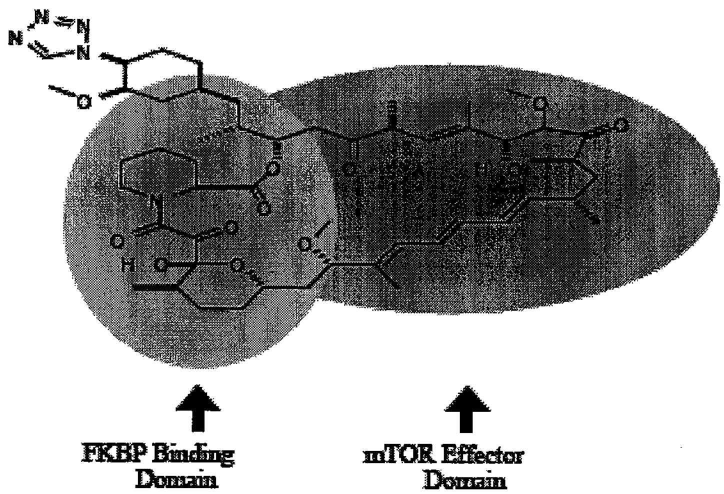


Figure 4-4: Suggested Mechanism of Action of Zotarolimus

Drugs of the limus family have been previously approved by FDA. For example, rapamycin (sirolimus) is the one limus drug approved for application on a drug eluting stent and is also approved as co-medication for renal transplant immunosuppression. Zotarolimus is a cytostatic cell cycle inhibitor that inhibits cells from entering the S phase of mitosis, as shown in Figure 4-5.

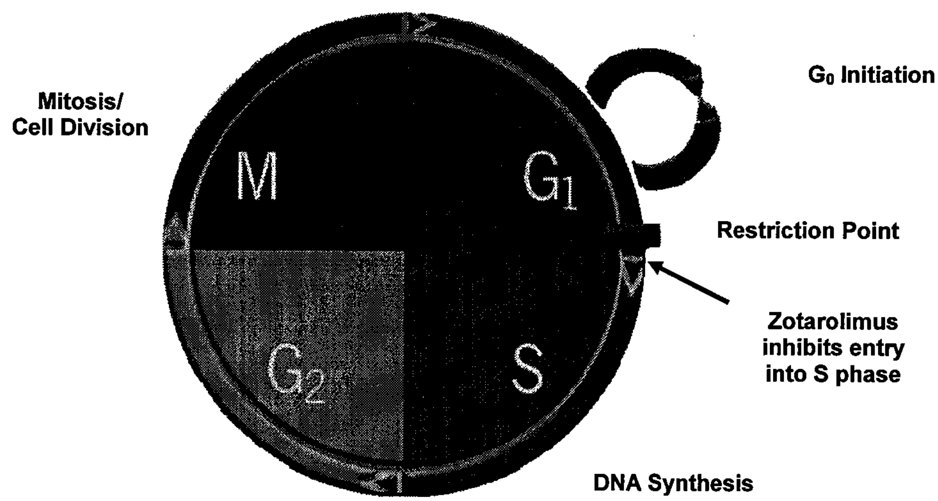


Figure 4-5: Cytostatic Cell Cycle Inhibition

Table 4-2 below shows measures of lipophilicity and potency for the limus family of drugs involved in drug-eluting stent applications. The low nanomolar concentration in the tissue would indicate little anticipated difference in the tissue effect for the differences in IC50. Also of note, zotarolimus is highly protein bound in man, distributed to the whole blood with a red blood cell-to-plasma appropriation of 20:1. The drug is not available as an oral formulation and when administered via stent or IV formulation, is metabolized and excreted primarily by the liver. Radiolabel studies in several species including man confirm approximately 84% excretion through the liver and gut, with only approximately 6% by renal excretion.

Table 4-2: Lipophilicity and Potency of Limus Family Drugs

	Rapamycin	Zotarolimus
Lipophilicity	logD 3.6	logD >4.5
Potency	IC50 0.4nM	IC50 0.3nM

By replacing the hydrophilic hydroxyl group with a lipophilic tetrazole group, the drug substance zotarolimus becomes substantially more lipophilic than sirolimus, thereby increasing its tissue retention time. Although there has been a lot of focus on the elution curves associated with many drug eluting stents, the important measure is time in tissue discussed below.

Lipophilicity is demonstrated by very high octanol: water partition coefficient (>4.5 at pH 6.5 and pH 7.4), represented as follows:

$$\mathrm{Log10}D = \mathrm{Log10}P_{\mathrm{octanol/pH\ 7.4\ buffer}}$$
$$=> 4.5, \text{ indicative of high lipophilicity.}$$

The lipophilic properties of zotarolimus are thought to enhance absorption of the drug across the cellular membrane of target tissues. Limited water solubility (0.47 µg/ml at pH 6.5 and 0.53 µg/ml at pH7.4) is highly amenable to the design of a drug-coated stent, in that low water solubility may impede systemic distribution from the stent. In addition, the lipophilic character of zotarolimus may favor an ability to cross cell membranes to inhibit neointimal proliferation of target tissue and be retained in tissue longer than less lipophilic drugs. Consequently, despite the fact that zotarolimus elutes from the stent within 14 days, it remains in tissue at detectable levels up to 28 days. Reference Figure 4-6 and Figure 4-7 below for curves generated from studies of porcine drug elution kinetics and pharmacokinetics.

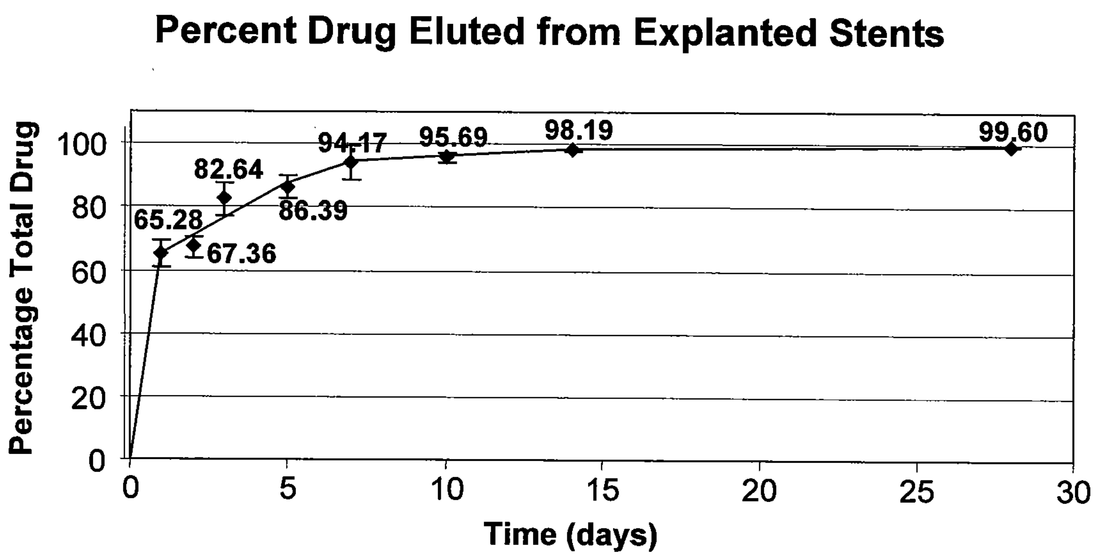


Figure 4-6: Percent Drug Eluted from Explanted Stents

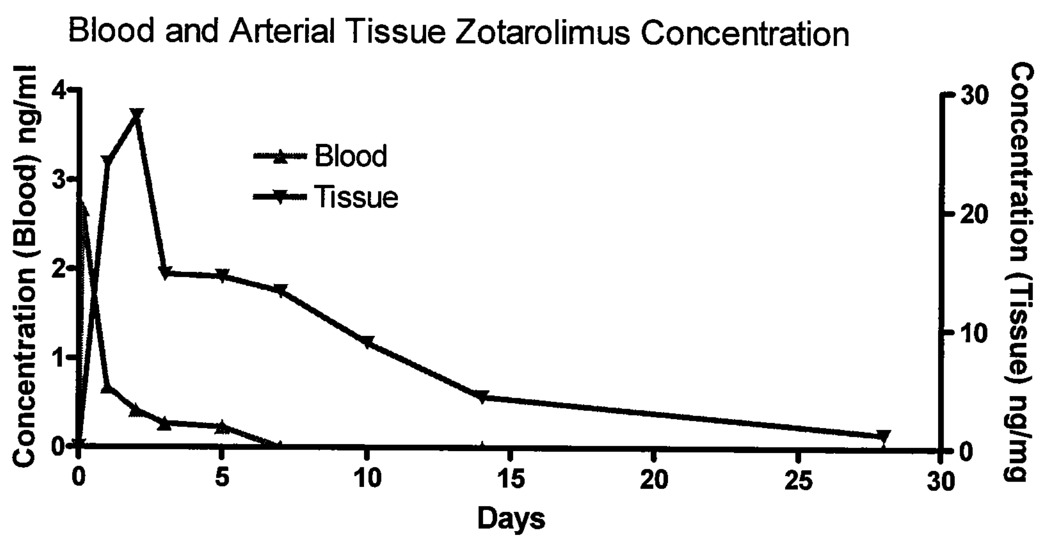


Figure 4-7 Blood and Arterial Tissue Zotarolimus Concentration

4.3.1 Studies of the Drug Substance (Zotarolimus)

The standard ICH-required battery of tests for a new chemical entity were performed in the development of zotarolimus. Testing performed on the drug substance is appropriate to the duration and levels of exposure in the Endeavor product. The drug substance testing most relevant to the DES application includes: 1) toxicological studies across multiple species including primates to define the margins of safety to the drug substance; 2) definition of metabolic pathways (CYP3A4) with no evidence of the drug interfering with the CYP3A4 pathway and lack of amplification (less than 2x) with co-administered ketoconazole, hence low opportunity for drug to drug interactions; and 3) identification of the metabolites and routes of excretion using radiolabeled drug across species, including man. In addition, a study was conducted in which approximately 100-fold drug exposure above anticipated clinical levels demonstrated that there was no impact of zotarolimus on stimulated platelet aggregation. Hence, the potential for alteration of platelet adhesion and aggregation is low.

Table 4-3 provides a list of the *in vitro* and *in vivo* pharmacological studies conducted on zotarolimus to confirm mechanisms of action, potency, toxicological effects, and to characterize the drug substance.

Table 4-3: Studies Supporting Zotarolimus Safety and Efficacy

Test	Test Strain	Administration
1. Mechanism and Interaction Studies		
FKBP-12 Affinity	PBMC, mice and rat-derived lymphocytes	in vitro
Concanavalin A-induced T-Cell Proliferation	PBMC, mice and rat-derived lymphocytes	in vitro
Mixed Lymphocyte Reaction	PBMC, mice and rat-derived lymphocytes	in vitro
Effect of PC-1036 on the Inhibition of IL-2 Secretion in Activated Human CD4+ T-Helper Cells	PBMC	in vitro
Effect on Human Platelet Function in Whole Blood	Human platelets	in vitro
Effect of BHT on Inhibition of Human Coronary Artery Smooth Muscle Cell Proliferation in Vitro	Human smooth muscle cells	in vitro
Comparative Potency in Inhibiting Human Coronary Artery Smooth Muscle Cell Proliferation	Human smooth muscle cells/endothelial cells	in vitro
Various Receptor Binding Assays	Radioligand binding method	in vitro
2. Pharmacological Safety Studies		
Effect on the Central Nervous System	SD rats	intravenous
Effect on the Central Nervous System	Wistar rats	oral
Effect on the Respiratory System	Wistar rats	intravenous
Cardiovascular functions/hematology tests (hematocrit)/body temperature	Wistar rats	intravenous
Cardiovascular functions/hematology tests/clinical chemistry tests	Wistar rats	intravenous
Cardiovascular functions (heart rate, blood pressure)	Wistar rats	intravenous
Effects on *HERG* Current	HEK293 cells	In vitro
Effects on Purkinje Fiber Repolarization	Beagles	In vitro

This standard battery of tests failed to demonstrate any concerns regarding cardiovascular, respiratory, or central nervous system effects.

4.3.2 Toxicity Studies

Table 4-4 below list the toxicity and toxicokinetic evaluations conducted to support the safety of zotarolimus.

Table 4-4: Single and Repeat Dose Toxicity Assays, Reproductive Toxicity Assays, Genotoxicity and Other Assays

Test	Test Strain	Administration	Administration Period	Amount Administered (µg/kg)
Single Dose Administration Toxicity Assays	SD Rats	Intravenous	-	3, 8, 25, 75
	Cynomolgus Monkeys	Intravenous	-	8, 25, 75
Repeat Dose Administration Toxicity Assays	SD Rats	Intravenous	28 days	3, 8, 25
	SD Rats	Intravenous	28 days	10, 30, 100
	Cynomolgus Monkeys	Intravenous	28 days	3, 8, 25
	Cynomolgus Monkeys	Intravenous	28 days	10, 30, 100
Testicular Toxicity Assay	SD Rats	Intravenous	70 days	3, 10, 30, 100
Genotoxicity Assays	S.typhimurium/ E.coli	In Vitro	-	-S9: 33.3-5, 000µg/plate +S9: 33.3-5, 000µg/plate
			-	-S9: 50-5, 000µg/plate +S9: 50-5, 000µg/plate
	Human lymphocytes	In Vitro	-	-S9: 12.5-800µg/mL +S9: 12.5-800µg/mL
			-	-S9: 25-125µg/mL +S9: 25-125µg/mL
	CD-1 Mice	Intravenous	2 days	0.85, 1.7, 3.4
Reproductive Development Toxicity Assays	SD Rats	Intravenous	G6-17	10, 30, 100, 300
	NZW Rabbits	Intravenous	G7-19	10, 30, 100, 300
	SD Rats	Intravenous	28 days	30, 100, 300
	SD Rats	Intravenous	14 days	30, 100, 300
	SD Rats	Intravenous	G6-17	10, 25, 60
	NZW Rabbits	Intravenous	G7-19	10, 30, 100
Local Stimulus-induced Assays	Not conducted			
Other toxicity Assays Antigenicity Assays	Hartley Guinea Pigs	Subcutaneous	Weekly intervals, 4 times	15, 30
	CBA/J Mice	Applied	3 days	10, 25, 50%

Based on the results of the studies listed above, zotarolimus was demonstrated to be safe for use as a coating on an implanted coronary stent.

4.3.3 ADME and Pharmacokinetic Testing

A number of studies were conducted to study the absorption, distribution, metabolism and excretion (ADME) of zotarolimus. Table 4-5 lists the ADME studies conducted, followed by a brief summary of some of the findings from these studies.

Table 4-5: ADME Studies Conducted on Zotarolimus

Test	Test Strain	Administration	Amount administered/ concentration of additive
1. Absorption			
1) Concentration in the blood for single dose administration	Mice/Rats	Intravenous/ oral	2.5mg/kg
	Rabbits	Intravenous	1mg/kg
	Pigs	Intravenous	1.0mg 1mg/kg
	Monkeys	Intravenous/ oral	2.5mg/kg • 1mg/kg
2. Distribution			
1) Histological Distribution	Rats	Intravenous	2.5mg/kg • 1mg/kg
	Rabbits	Intravenous	0.5mg/kg
2) Plasma Protein Binding	Rabbits/Dogs/Pigs/Humans	in vitro	300, 3, 000ng/mL
	Mice/Rats/ Dogs /Monkeys/ Humans	in vitro	10, 25, 50, 100, 500, 1, 000ng/mL
	Humans/HSA binding/AAG binding	in vitro	10, 25, 50, 100, 500, 1, 000ng/mL
3) Transition to Blood Cells	Humans	in vitro	1, 5, 10, 50, 100, 1, 000ng/mL
3. Metabolism			
1) Metabolites in the blood and plasma	Rats	Intravenous	2.5mg/kg • 1mg/kg
	Rabbits		0.5mg/kg
	Pigs/Monkeys		1mg/kg
	Humans		0.8mg
2) Metabolites in the urine and feces	Rats/Pigs/Monkeys	Intravenous	1mg/kg
	Humans		0.8mg
3) Metabolism in Hepatocytes	Rats/Dogs/Monkeys/Humans	in vitro	5µM (4, 831ng/mL)
4) Metabolism in Liver Microsomes	Humans	in vitro	5µM • 10µmol/L
5) Cytochrome P450 Inhibition	Humans	in vitro	66-6, 645ng/mL• 50-5, 000ng/mL
6) Study of the Metabolic	Humans	in vitro	25µM

Table 4-5: ADME Studies Conducted on Zotarolimus

Test	Test Strain	Administration	Amount administered/ concentration of additive
Pathway			
4. Excretion			
1) Excretion in the urine and feces	Rats	Intravenous	2.5mg/kg • 1mg/kg
	Rabbits		0.5mg/kg
	Monkeys		1mg/kg
2) Excretion in the bile	Rats	Intravenous	2.5mg/kg
5. Pharmacokinetic Drug-to-Drug Interactions			
Pharmacokinetics of combined used with Ketoconazole	Dogs	Intravenous Oral (Ketoconazole)	2.5mg/kg 35mg x 2 times/day drug combined with (Ketoconazole)
6.Other Assays			
Assay to Study 28-day Elution from Stents	Rabbit Illiac Arteries	in vivo	10µg/mm

The absorption following single dose intravenous administration of zotarolimus to mice, rats and monkeys was rapid and the maximum blood drug concentration was observed within one hour following administration.

The mean blood-to-plasma ratio of concentration following single dose intravenous administration of ^{3}H-labeled zotarolimus to monkeys and swine increased, indicating a substantial amount of radioactivity bonds with the blood cell component.

The assay to study the protein-binding of zotarolimus in the plasma of mice, rats, dogs and humans suggested that a clinical concentration (less than 25 ng/mL) of zotarolimus has a protein-binding affinity of 97% or more in human plasma. While zotarolimus exhibited a high binding affinity to HSA and AAG, it binds to a greater extent with blood cells (the *in vivo* blood-to-plasma ratio is 20:1). Therefore, the drug-protein interaction with HSA and AAG is not considered to have a significant effect on the systemic concentration of circulating zotarolimus from a clinical standpoint.

The mean zotarolimus blood concentration time profile following IV-bolus administration is at least biphasic, with the terminal phase becoming evident after the distribution phase at about 8 hours post-administration. Zotarolimus is distributed to a greater extent in the cellular fraction of the whole blood than in plasma and is extensively bound to plasma proteins in healthy subjects.

Metabolism is oxidative in the liver, and enzymes of the CYP3A family are the major catalysts of oxidative metabolism of zotarolimus. Zotarolimus is a competitive inhibitor of CYP3A-dependent activities; however, the IC50 values (3 µM and above) are many fold higher than the systemic concentrations following stent implantation, and the

potential for interaction with co-administered drugs is low. Co-administration with ketaconazole demonstrates little amplification of the zotarolimus exposure as a result of ketakonazole inhibition of zotarolimus metabolism through the CYP3A4 pathway. In two different species, the increase in zotarolimus exposure is less than two fold (less than the five-fold or greater amplification usually associated with a significant effect).

Following IV infusion of [^{3}H] zotarolimus, the majority of the circulating activity was due to the parent drug as the profiling of the blood samples showed metabolites contributing no more than 0.2%. These results suggest that following an IV dose, zotarolimus is taken up and bound by the blood cells with little free drug available. This binding and the subsequent slow release of the zotarolimus into the plasma over time appear to prevent rapid metabolism.

Elimination of [^{3}H] zotarolimus through the urine was about 6% of the dose (Study M03-646) over 216 hours after IV administration and about 82% in the feces over 288 hours. Over the course of the study (288 hours), 88% of administered radioactivity was accounted for. Dose proportionality assessments were made for single and multiple IV doses of zotarolimus in these Phase 1 studies.

Overall, these studies indicate that the pharmacokinetics of zotarolimus are essentially dose proportional over the single dose range of 100 to 900 µg and 14-day QD multiple dose range of 200 to 800 µg. Additionally, zotarolimus pharmacokinetics are time linear over the studied 14-day QD multiple dose range of 200 to 800 µg. Clearance showed a difference between IV-bolus and IV-infusion administration and was partly due to zotarolimus adsorption (9-12%) to the infusion sets during IV infusion and could partly be due to the difference in the rate at which the drug is sequestered in blood cells following administration.

4.3.4 Clinical Studies of the Drug Substance

Single and repeat dose administration assays were conducted to evaluate the safety, tolerability and pharmacokinetics of intravenous administration of zotarolimus in healthy subjects. Administration doses were selected based on the anticipated stent dosage (10µg/mm) and the results of the animal safety testing. Dose escalation was performed with subject safety a priority. Dosing began at the lowest dosage, and dose administration followed only after safety was confirmed at the previous dose, consistent with most early pK studies in man. The drug is formulated with propylene glycol with World Health Organization (WHO) limits to the maximum amount to be administered daily. The single dose administration given was to the maximum allowable dose per day based on these WHO and ethics committee guidelines. The subsequent multiple dose study included a dose that was slightly under the maximum daily limits for the 14 days of multiple infusions.

The safety and pharmacokinetics of intravenous zotarolimus administration have been investigated in four Phase 1 studies.

Study <u>M01-336</u> was a randomized, double-blind placebo controlled study, to evaluate the safety, tolerability and pharmacokinetics of IV bolus doses of zotarolimus from 100 to 900 µg administered to 40 of 60 healthy adult male subjects. The study concluded that there were no apparent differences among the doses with regard to safety and no serious

adverse events. The treatment emergent adverse events included mostly injection site complaints with the rapid bolus injection of a very high osmolality drug solution.

Because of the issues with the formulation of the drug and the injection site complaints, the multidose study below allowed for a push of the drug through a side branch arm to the IV given slowly, over an hour. This avoided many of the complaints associated with the rapid injection of the drug in the single dose rapid bolus administration. Because of the high lipophilicity, high osmolality, and formulation issues, the subsequent set of studies mandated careful planning for data collection and avoidance of IV formation-related issues.

Study M02-501 was a randomized, double-blind, placebo controlled study to evaluate the safety, tolerability, pharmacokinetics, potential immunosuppressive and QT effects of zotarolimus. Fourteen consecutive days of IV dosing with zotarolimus included doses of 200, 400 and 800 µg administered over by IV side branch injection over 1 hour in 48 of 72 healthy adult subjects. There were no deaths or other serious adverse events. Results of other safety analyses including individual values for vital signs, laboratory safety assessments and physical exams were unremarkable for each treatment group. Additionally, the proportion of subjects reporting treatment-emergent adverse events was similar among the zotarolimus and placebo groups with no statistically significant mean differences seen related to QT_c interval prolongation between the 800 µg dose group and placebo. Additionally, there were no significant trends found related to dose on either Study Day 1 or 14 and no positive correlation between changes from baseline QT_c interval with the individualized correction method and plasma concentration of zotarolimus. The study confirmed the pharmacokinetics of zotarolimus seen in the single dose study, providing predictable kinetics with linear and dose-proportional findings. The multiple dose also confirmed the steady state achievement at day 10 of daily dosing. In addition and in general, all evaluated immunological markers showed unremarkable differences in treatment groups as compared to placebo over time. The study report indicates the drug does not appear to affect the immunocompetency of the healthy subjects over the studied doses and over the study period (44 days), a conclusion supported by the absence of any clinical connection.

The two pharmacokinetic studies above provide the bulk of the human exposure of the drug substance not associated with the stent drug combination product known as Endeavor. This exposure provides the basis for the kinetics of the drug, also confirmed with drug/stent elution pharmacokinetics and gives the basis for the calculation of the systemic drug exposure margins of safety. The Cmax achieved with the single bolus dose provided the highest Cmax and is approximately 25-fold the exposure anticipated in patients with 48 mm of stent length. In addition, the prolonged daily exposure in the multiple dose study provides human AUC exposure margins of approximately 15-fold for 48 mm of stent length.

Study M03-646 was a single-dose, open-label study investigated the disposition of [^{3}H] zotarolimus in 5 healthy adult male subjects. One subject received a single 3-minute IV bolus of 800 µg (200 µg/mL) and four subjects received a single 60-minute infusion of 800 µg (200 µg/mL) of [^{3}H]- zotarolimus. The results demonstrated that the dosing regimen was generally well tolerated. Two subjects reported adverse events including one severe reaction that was vasovagal in origin and possibly related to study drug.

Concentrations of total blood radioactivity measured in this study were similar to zotarolimus concentrations in previous Phase 1 studies. A comparison of the plasma and blood concentrations indicates an association of the radiolabel with red blood cells. Total radioactivity was quantitatively recovered and slowly eliminated in the urine and feces over the collection period, with the main route of excretion via the feces, with limited renal excretion (6%), and little drug not ultimately accounted for.

Study M03-653 was a sequential, single dose, open-label study conducted in 18 healthy adult subjects to evaluate the effect of the CYP3A inhibitor, ketoconazole on the pharmacokinetics of zotarolimus (which is metabolized by CYP3A4) and to assess the safety and tolerability of zotarolimus (400 µg via 60-minute infusion on Days 1 and 10) when co-administered with ketoconazole (200 mg orally BID on Study Days 6-14). The results indicated that zotarolimus alone and administered with ketoconazole were generally well tolerated. No deaths or other serious adverse events were reported. Seven of 18 subjects (39%) reported at least one treatment-emergent event, the most common (reported in two or more subjects) were headache and sore throat. The zotarolimus exposure when co-administered with ketoconazole was amplified less than two-fold and did not reflect a significant drug-to-drug interaction.

In summary, among all subjects who participated in the four Phase 1 studies using zotarolimus, no clinical or biochemical evidence of immunosuppression or clinically significant electrocardiographic findings were found. Additionally, the most commonly experienced treatment-emergent adverse events among zotarolimus treated subjects were injection site reaction, pain and headache. The percentages of subjects reporting adverse events were similar between those receiving zotarolimus and those receiving placebo. The majority of the adverse events in the four clinical pharmacology studies were mild to moderate in severity. The studies characterized the drug's linear and dose proportional kinetics, provided margins of safety for a 48 mm stent, and confirmed the lack of significant drug exposure amplification with co-administered drugs metabolized through the CYP3A4 path. Many cardiovascular drugs are metabolized through the same pathway and the data indicate the minimal potential for interaction toxicity.

The combination of *in vitro*, *in vivo* animal and human studies confirm the drug ADME, toxicology and kinetics and characterize the molecule, zotarolimus.

4.4 Endeavor Non-Clinical Studies

A series of non-clinical laboratory studies were performed, pertaining to the stent and the stent delivery system (i.e. the stent mounted on either the Endeavor OTW, RX and MX^2 stent delivery system), the polymer substance [i.e., Phosphorylcholine (PC)], the drug substance (i.e., zotarolimus), and the finished combination product (i.e., Endeavor Zotarolimus-Eluting CSS). Following is a listing of the non-clinical design verification testing performed.

Table 4-6: Overview of Non-Clinical Testing

	Test	Description
Functional Design Verification and Shelf Life Testing	Material Characterization	Material characterization of the Endeavor bare metal stent and delivery system components per FDA January 13, 2005 Guidance (Part A)
	Stent Dimensional and Functional Attributes	Evaluation of Endeavor stent dimensional and functional attributes per FDA January 13, 2005 Guidance (Part B)
	Delivery System Dimensional and Functional Attributes	Evaluation of Endeavor delivery system dimensional and functional attributes per FDA January 13, 2005 Guidance (Part C)
	Functional and Dimensional Shelf life Testing	Evaluation of the Endeavor stent and delivery system Functional and Dimensional attributes post aging
Analytical/ Coating Integrity and Stability Testing	Drug Coating Integrity and Analytical Testing	Evaluation of the analytical and coating integrity attributes of the Endeavor stent per FDA January 13, 2005 Guidance
	Stability Testing	Evaluation of the analytical and coating integrity attributes of the Endeavor stent and integrity of the primary packaging per ICH Q1A
Elution	Elution Method Development	Elution Assay was developed to measure the *in vitro* release kinetics of zotarolimus from the Endeavor stent system
Packaging Integrity	Packaging Integrity Testing	Evaluation of packaging integrity per ISO 11607

The following standards and guidance documents were considered in the development of test plans used in non-clinical testing of the Endeavor Zotarolimus-Eluting CSS. Appropriate rationales are provided to justify any deviations from testing standards or guidance listed.

Table 4-7: Guidance Documents Considered

Guidance for Industry and FDA staff:	Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, January 2005
Guidance for Industry:	SUPAC-MR: Modified Release Solid Oral Dosage Forms. Scale-UP and Postapproval Changes: Chemistry. Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, September 1997
ICH Q1A (R2)	Stability testing of new drug substances and product, ICH August 2001
ICH Q1B	Photostability Testing of New Drug Substances and Products, November 1996
ICH Q1D	Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products, January 2003
ICH Q1E	Evaluation of Stability Data, June 2004
ICH Q2A	Text on Validation of Analytical Procedures, March 1995
ICH Q2B	Validation of Analytical Procedures: Methodology, May 1997
ICH Q3B(R)	Impurities in New Drug Products (Revision 2), August 2006
ICH Q3C	Impurities: Residual Solvents, December 1997
ICH Q6A	International Conference on Harmonization; Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, December 2000
FDA CDER Guidance for Industry	Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997
FDA CDER Guidance for Industry	Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro/In Vivo* Correlations, September 1997
FDA CDER Guidance for Industry	Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations, March 2003
Guidance for Industry:	Statistical Approaches to Establish Bioequivalence, January 2001
21 CFR §58	FDA Good Laboratory Practices (GLP) regulations
Guideline	FDA Guideline on Validation of the Limulus Amebocyte Lysate test as an end –product Endotoxin test for human and animal parenteral drugs, biological products and medical devices, December 1987

Table 4-8: Product Standards

ASTM E8	Standard Test Methods for Tension Testing of Metallic Materials, April 2004
ASTM E112	Standard Test Methods for Determining Average Grain Size, November 2004
ASTM E384	Microindentation Hardness of Materials, August 2005
ASTM F562	Standard Specification for Wrought Cobalt-35 Nickel-20 Chromium-10 Molybdenum Alloy (UNS R30035), April 2002
ASTM F688	Standard Specification for Wrought Cobalt-35 Nickel-20 Chromium-10 Molybdenum Alloy Plate, Sheet, and Foil for Surgical Implants (UNS R30035), August 2005
ASTM E45	Inclusion content in steel, November 2005
ASTM F2052	Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment, March 2006
ASTM F2119	Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants, June 2001
ASTM F2182	Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging, November 2002
ASTM F2213	Standard Test Method for Measurement of Magnetically Induced Torque on Passive Implants in the Magnetic Resonance Environment, May 2006
ASTM F2129	Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices, May 2006
ASTM F746	Standard Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials, October 2004
ASTM G71	Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes, October 2003
ASTM F2079	Standard Test Method for Measuring Intrinsic Elastic Recoil of Balloon-Expandable Stents, January 2001
ASTM F2081	Standard Guide for Characterization and Presentation of the Dimensional Attributes of Vascular Stents, September 2006
EN 14299	Non Active Surgical Implants-Particular Requirements for Cardiac and Vascular Implants-Specific Requirements for Arterial Stents, August 2004
ISO 10555-1	Sterile, Single – Use Intravascular Catheters, General Requirements, July 2005

Table 4-9: Packaging Standards

EN 868	Packaging Materials and Systems for Medical Devices which are to be sterilised, August 1999
ANSI/AAMI/ISO 11607	Packaging for Terminally Sterilized Medical Devices, July 2004
ASTM D3985	Oxygen Gas Transmission Rate Through Plastic Film and Sheeting using a Coulometric Sensor, June 2005
ASTM D4169	Practice for Performance Testing of Shipping Containers and Systems, October 2005
ASTM D6653	Test Method for Determining Effects of High Altitude on Packaging Systems by Vacuum Method, April 2001
ASTM F88	Test Method for Seal Strength of Flexible Barrier Materials, April 2006
ASTM F1249	Water Vapor Transmission Rate Through Plastic Film and Sheeting Using a Modulated Infrared Sensor, June 2006
ASTM F1980	Standard Guide for Accelerated Aging of Sterile Medical Device Packages, January 2002
ASTM F2096	Test method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test), April 2004
ASTM D4332	Practice for Conditioning Containers, Packages, or Packaging Components for Testing, April 2001
ASTM D999	Standard Test Method for Vibration Testing of Shipping Containers, April 2001
ASTM F1929	Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration, November 1998
ASTM D5276	Test Method for Drop Test of Loaded Containers by Free Fall, April 1998
ASTM D642	Test Method for Determining Compression Resistance of Shipping Containers, Components, and Unit Loads, June 1994
ASTM D4728	Test Method for Random Vibration Testing of Shipping Containers, April 2001

Table 4-10: Labelling Standards

EN980	Graphical Symbols for Use in the Labeling of Medical Devices, September 2006
EN 1041	Terminology, Symbols and Information provided with Medical Devices – Information supplied by the Manufacturer with Medical Devices, April 1998
ISO15223	Medical Devices – Symbols to be used with Labels, Labelling and Information to be Supplied, April 2000
ASTM F2503	Standard Practice for Marketing Medical Devices and Other Items for Safety in the Magnetic Resonance Environment, August 2005

Table 4-11: Biocompatibility Standards

ISO10993-01	Biological Evaluation of Medical Devices, October 1997
ISO10993-01	Biological Evaluation of Medical Devices, August 2003
Blue Book Memorandum G95-1	Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices, May 1995

Table 4-12: Sterilization Standards

EN550	Sterilization of medical devices- validation and routine control of ethylene oxide sterilization of health care products – Requirements for validation and routine control – EtO sterilization, November 1994
EN556-1 2002 + A1 2002	Sterilization of Medical devices-Requirements for Medical Devices to be designated "Sterile" – Part 1: Requirements for terminally sterilized medical devices, 2002
ISO 11138-1	Sterilization of Health care products – Biological Indicators – Part 1: General, October 1994
ISO 11138-2	Sterilization of Health care products – Biological Indicators – Part 2: Biological Indicators for Ethylene Oxide Sterilization, October 1994
ISO 11135	Medical Devices – validation and routine control of ethylene oxide sterilization, February 1994
ISO 11737-1	Sterilization of health care products – Microbiological methods – Part 1: Estimation of population of micro-organisms on products, August 2006
ISO 11737-2	Sterilization of health care products – Microbiological methods – Part 2: Tests of sterility performed in the validation of a sterilization process, July 1998
ISO10993-7	Biological evaluation of medical devices- Ethylene oxide sterilization residuals, October 1995
USP 29	United States Pharmacopoeia 29 – National Formulary 24, 2006
EP 2005	European Pharmacopoeia 5th edition, January 2005
AAMI/ST72	Bacterial Endotoxins – Test methodologies, routine monitoring and alternatives to batch testing, September 2002
AAMI TIR19	Guidance for ANSI/AAMI/ISO 10993-7 1995. Biological Evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals, 1998/ A1:1998
ANSI/AAMI TIR No. 15	Ethylene oxide sterilization equipment, process considerations, and pertinent calculations, 1997
AAMI TIR14	Contract Sterilisation for Ethylene Oxide, 1997/ A1:2004
AAMI TIR16: 2000	Process Development and Performance Qualification for Ethylene Oxide sterilisation – Microbiological aspects, March 2000

Table 4-12: Sterilization Standards

EN886-1	Biological Systems for testing sterilizers and sterilization processes- Part 1 – General requirements, November 1997
ISO10993-7	Biological evaluation of medical devices- Ethylene oxide sterilization residuals, October 1995

4.4.1 Biocompatibility Studies

A series of GLP biocompatibility tests and USP Physicochemical tests were conducted to demonstrate that the components of the Endeavor Zotarolimus-Eluting Coronary Stent System (OTW, RX and MX^2) are non-toxic. Tests were conducted on ethylene oxide-sterilized Endeavor coated stents, stent delivery systems (finished product) and polymer-only coated stainless steel (SS) coupons. These test articles were processed in the same manner as the finished Endeavor product. The polymer only coated coupons did not include drug substance but were manufactured to simulate the processing of Endeavor stents with equivalent surface treatment, cross-linking and sterilization processes utilized. In all of these test systems, the materials were non-reactive and met all acceptance criteria. The results of the biocompatibility studies indicated that the Endeavor Zotarolimus-Eluting CSS was biologically safe and acceptable for clinical use.

Table 4-13: Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Result
Cytotoxicity	ISO 10993-5: *In Vitro* Cytotoxicity (L929 MEM Elution)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-cytotoxic)
Pyrogenicity	ISO-10993-11: Systemic Toxicity (Material Mediated Rabbit, Injection)	• Endeavor stent and delivery systems	Pass (non-pyrogenic)
Sensitization	ISO-10993-10: Sensitization (Guinea pig Maximization)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-sensitizing)
Acute Intracutaneous Reactivity	ISO-10993-10: Irritation (Injection)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non- irritant)
Acute Systemic Toxicity	ISO-10993-11: Systemic Toxicity (Acute)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-toxic)
Hemocompatability	ISO-10993-4: *In Vivo* Thromboresistance	• Endeavor stent and delivery systems	Pass (non-thrombogenic)
	ISO-10993-4: C3a Complement Activation (*In Vitro*)	• Endeavor stent and delivery systems	Pass (non-complement activating)

Table 4-13: Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Result
Hemocompatability	ISO-10993-4: SC5b9 Complement Activation (*In Vitro*)	• Endeavor stent and delivery systems	Pass (non-complement activating)
	ISO-10993-4: Plasma Recalcification	• Endeavor stent and delivery systems	Pass (no significant change in coagulation time)
	ISO-10993-4: *In Vitro* Hemolysis Study	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-hemolytic)
	ISO-10993-4: White Blood Cell Morphology	• Endeavor stent and delivery systems	Pass (no change in WBC morphologically)
Genotoxicity	ISO-10993-3: Bacterial Reverse Mutation (AMES)	• Endeavor stent	Pass (non-mutagenic)
	ISO-10993-3: *In Vitro* Chromosomal Aberration in Mammalian Cells	• Endeavor stent	Pass (non-clastogenic)
	ISO-10993-3: *In Vivo* Mouse Bone Marrow Micronucleus Test	• Endeavor stent	Pass (non-mutagenic)
Material Characterization (USP Physicochemical Testing)	USP Physicochemical Extracts <661> (Aqueous)	• Balloon Material • Polyethylene Sheath • PC Polymer-only Coated Coupons	Pass

4.4.2 Pre-clinical Studies

Detailed arterial histopathology and histomorphometry are not obtainable through human clinical trials; therefore, a series of animal studies were conducted to evaluate safety, proof of concept and overall product performance.

Medtronic Vascular conducted a series of animal studies evaluating a variety of Zotarolimus-Eluting stent formulations (e.g., various drug dosages), polymer-coated control stents and/or bare metal control stents. These studies were conducted in coronary arteries of pigs, or iliac arteries of rabbits. Data from these studies served as the basis for the dose selection for the Endeavor Zotarolimus-Eluting CSS used in the Endeavor clinical studies.

The intravascular safety and biocompatibility of zotarolimus-eluting stents were evaluated in a series of animal studies in a porcine model of stent mediated vascular injury. Time points evaluated include 7, 28, 90, and 180 days. In addition, drug content was evaluated at 1, 2, 3, 5, 7, 10, 14 and 28 days. All study phases (feasibility, safety,

pharmacokinetic and acute) are represented by studies that were conducted in accordance with § 21CFR 58 (Good Laboratory Practices), except where noted and the methods described by the Schwartz et al article entitled "*Drug-Eluting Stents in Preclinical Studies – Recommended Evaluation from a Consensus Group*."[38] The results of these studies support the safety and biocompatibility of the Endeavor Zotarolimus-Eluting CSS. Summaries of the major animal studies performed to support product safety are included in Table 4-14 below.

[38] Schwartz RS, Edelman ER, Carter A, Chronos N, Rogers C, Robinson KA, Waksman R, Weinberger J, Wilensky RL, Jensen DN, Zuckerman BD, Virmani R; Consensus Committee. Drug-eluting stents in preclinical studies: recommended evaluation from a consensus group. Circulation. 2002 Oct 1;106:1867-1873.

Table 4-14: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
FS102	Test Article: Zotarolimus-eluting Endeavor stent, 5 and 10 µg/mm doses Control: BMS* GLP: Yes	Diameter: 3.0, 3.5, 4.0 mm Lengths: 12, 18 mm	Domestic Swine Test and Control: 15 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control	Test: 32 Control: 20	7 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Cell proliferation Acute delivery
FS135	Test Article: Zotarolimus-eluting Endeavor stent, 10 and 30 µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.25, 2.5mm Lengths: 8 mm	Juvenile Yorkshire Swine Test and Control: 21 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 24 Control: 20 Control (Polymer Coated Stents): 12	28 days	Angiographic patency Histologic and histomorphometric evaluation Acute Delivery Chronic vascular response at 28 days
FS99	Test Article: Zotarolimus-eluting Endeavor stent, 1, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12, 18 mm	Domestic Swine Test and Control : 51 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control.	Test: 99 Control: 64 Control (Polymer Coated Stents): 13	28 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 28 days

* BMS = bare metal stent – Driver for these studies.

Table 4-14: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
FS100	Test Article: Zotarolimus-eluting Endeavor stent, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12mm	Yucatan Miniswine Test & Control: 31 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control.	Test: 58 Control: 43 Control (Polymer Coated Stents): 9	90 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 90 days
FS101	Test Article: Zotarolimus-eluting Endeavor stent, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12mm	Yucatan Miniswine Test & Control: 30 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control.	Test: 55 Control: 40 Control (Polymer Coated Stents): 11	180 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 180 days
FS114	Test Article: Zotarolimus-eluting Endeavor stent 10µg/mm dose GLP: Yes	Diameter: 3.0mm Lengths: 12mm	Domestic Swine (LAD, LCX, RCA) One stent per vessel.	48	1, 2, 3, 5, 7, 10, 14 and 28 days	Evaluation of drug release rate, arterial drug levels & systemic drug levels over time.
FS102	Test Article: Zotarolimus-eluting Endeavor stent 5 and 10 µg/mm doses Control: BMS* GLP: Yes	Diameter: 3.0, 3.5, 4.0 mm Lengths: 12, 18 mm	Domestic Swine Test and Control: 15 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control	Test: 32 Control: 20	7 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Cell proliferation Acute delivery

Table 4-14: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
FS135	Test Article: Zotarolimus-eluting Endeavor stent, 10 and 30 µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.25, 2.5mm Lengths: 8 mm	Juvenile Yorkshire Swine Test and Control: 21 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 24 Control: 20 Control (Polymer Coated Stents): 12	28 days	Angiographic patency Histologic and histomorphometric evaluation Acute Delivery Chronic vascular response at 28 days
FS99	Test Article: Zotarolimus-eluting Endeavor stent, 1, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12, 18 mm	Domestic Swine Test and Control : 51 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control.	Test: 99 Control: 64 Control (Polymer Coated Stents): 13	28 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 28 days
FS100	Test Article: Zotarolimus-eluting Endeavor stent, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12mm	Yucatan Miniswine Test & Control: 31 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control.	Test: 58 Control: 43 Control (Polymer Coated Stents): 9	90 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 90 days
FS101	Test Article: Zotarolimus-eluting Endeavor stent, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12mm	Yucatan Miniswine Test & Control: 30 (LAD, LCX, RCA) Single and overlapping stents	Test: 55 Control: 40 Control (Polymer Coated Stents): 11	180 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 180

Table 4-14: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
	GLP: Yes		Animals received both test and control.			days
FS114	Test Article: Zotarolimus-eluting Endeavor stent 10µg/mm dose GLP: Yes	Diameter: 3.0mm Lengths: 12mm	Domestic Swine (LAD, LCX, RCA) One stent per vessel.	48	1, 2, 3, 5, 7, 10, 14 and 28 days	Evaluation of drug release rate, arterial drug levels & systemic drug levels over time.

*BMS = bare metal stent – Driver for these studies.

Toxicity

The systemic toxicity of the intact Endeavor Zotarolimus-Eluting Coronary Stent System has been investigated in a number of studies that were intended principally to define the local tolerance and healing response to the implanted Endeavor Zotarolimus-Eluting Coronary Stent System (Studies FS97, FS99, FS100, FS101, FS102, FS110, FS124 and FS135). In these studies, animal survival, body weights, body temperature, total blood counts, liver function tests, serum creatinine, cholesterol, and triglycerides were evaluated before and at varying times (7, 28, 90, and 180 days) after implantation of stents. Also, animals were subject to complete necropsies at 7, 28, 90, and 180 days after stent implantation and in Studies FS99, FS100, FS101, FS107, FS124 and FS135, sections of spleen, liver, kidneys, and/or lungs were examined histopathologically.

All of the rabbits (n=45) and 206 out of 209 of the swine that were implanted with stents survived for the duration of the studies (Studies FS97, FS99, FS100, FS101, FS102, FS107, FS110, FS114, FS124 and FS135). A total of three deaths occurred in these studies. Two swine that died 24 hours after implantation were from the polymer group in FS100 and in the Endeavor 30ug/mm dose group from FS124. In addition, one pig in FS124 was euthanized at day 20 from the polymer group due to a respiratory infection. Necropsy and careful examination of the organs, including the heart from the spontaneous deaths revealed no obvious cause for these events. The stents in these animals had deployed successfully and the hearts showed no abnormalities. Consequently, these deaths are believed to be due to non-stent-related issues.

Body weight data, clinical laboratory measurements, necropsies, and histopathological examination of selected tissues from the animals implanted with stents demonstrated only infrequent adverse systemic effects and no effects that could be attributed to stent implantation. Furthermore, since animals were each implanted with both control bare Driver stents and one or more Endeavor Zotarolimus-Eluting Coronary Stent Systems, it was not possible to distinguish effects due to the product that is the subject of this submission (the Endeavor Zotarolimus-Eluting Coronary Stent System) or its comparator (the Driver stent). Overall, however, implantation of single or overlapped Driver and Endeavor Zotarolimus-Eluting Coronary Stent Systems (with zotarolimus coating doses as high as 30 µg/mm) yielded no significant adverse systemic effects.

Pharmacodynamics

Multiple considerations were applied during the finalization of the optimal dose. Medtronic's selection of dose was based upon measurement of drug concentration in tissue, pharmacological activity of zotarolimus on smooth muscle cells level *in vitro* and *in vivo*, and a documented inhibition of porcine neointimal responses.

In vivo drug concentration and in vitro SMC studies

Medtronic has determined *in vivo* that the average arterial concentration of zotarolimus at 28 days post-stenting with a dose of 10 µg/mm is 1.18 ng/mg tissue (1180 ng/ml assuming 1 g/ml; FS114). Based upon the *in vitro* determination of SMC inhibition in vitro (EC_{50}= 2.9 nanomolar or 2.8 ng/ml), a sufficient concentration of drug is present for at least 28 days, to provide inhibition of neointimal proliferation with approximately a two hundred-fold margin (Comparison of Activity with Zotarolimus and other Drugs in Inhibiting Human Coronary Artery Smooth Muscle and Endothelial Cell Proliferation:

Abbott Study 51R-002-AP-03-R0). This study, when combined with the findings of arterial drug concentration, confirmed that a sufficient amount of drug was present to mediate a local therapeutic response at the targeted dose.

Smooth muscle cell proliferation
The efficacy of the zotarolimus incorporated into the coating of the Endeavor Zotarolimus-Eluting Coronary Stent System in inhibiting smooth muscle proliferation at the site of implantation has been examined in studies FS102 and FS107. In Study FS102, 7 days after implanting the Endeavor Zotarolimus-Eluting CSS into the coronary arteries of farm swine, animals were administered bromodeoxyuridine to identify proliferating cells and sacrificed 55-100 minutes later. There were significantly fewer proliferating cells found in sections of stented tissue when zotarolimus was incorporated into the stent coating than when bare Driver stents were implanted.

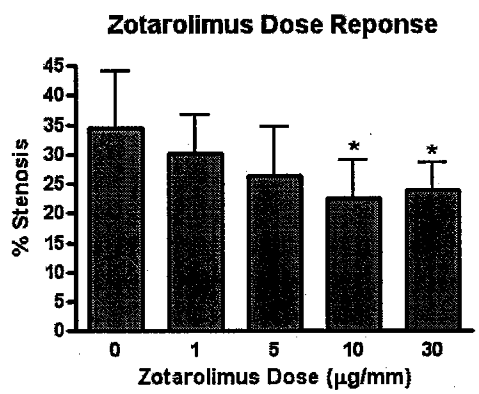
Table 4-15: Bromodeoxyuridine Results (Study FS102)

	Bromodeoxyuridine-positive cells/mm^2	Percent Bromodeoxyuridine-positive cells
Bare Driver stent (n=40 areas)	237.09 ± 224.21*	6.50 ± 6.40*
Endeavor 5 µg/mm (n=24 areas)	131.96 ± 125.46*	3.21 ± 2.81*
Endeavor 10 µg/mm (n=28 areas)	110.63 ± 134.86	2.77 ± 3.81

* p<0.05 versus bare control stents

These findings were confirmed in a rabbit iliac model of stent implantation (FS107). At 7 days after implantation, there were significantly fewer proliferating cells found in sections of stented tissue when zotarolimus was incorporated into the stent coating than when bare Driver stents were implanted. These findings of *in situ* inhibition of SMC proliferation are consistent with the anticipated response to drug in tissue.

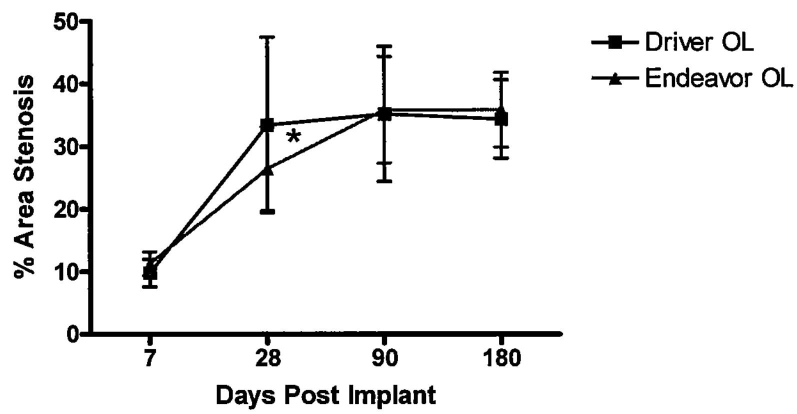
Neointimal Response
A multi-dose study of neointimal response to zotarolimus on the Endeavor stent in porcine coronary arteries (FS99) showed a trend for increased neointimal suppression when compared to the PC polymer control (0µg/mm zotarolimus dose) with increasing drug up to 10 µg/mm, supporting this target dose for clinical use (see below) and suggesting a potential for clinical utility.



0 dose = PC polymer only
*P<0.05 Relative to PC control by ANOVA with Dunnetts

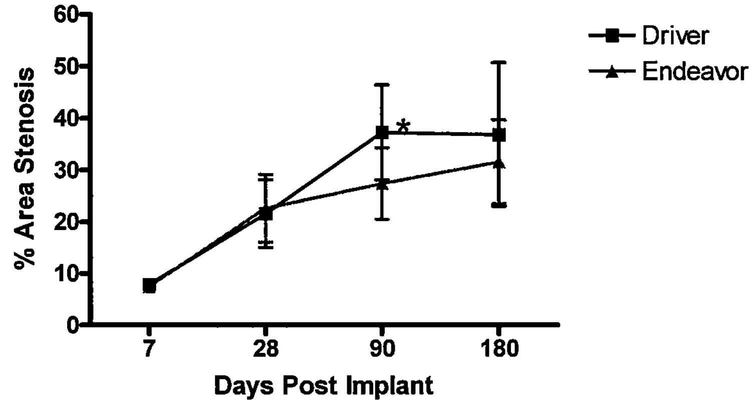
Examination of neointimal suppression relative to bare metal stents can best be observed over multiple time periods (below). While not the objective of these studies, significant inhibition of restenosis can be observed, resulting in blunting of the neointimal response at the 28 day (overlapped stents) and 90 day (single stents) time points.

Overlapped Stents



* P<0.05

Single Stents



* P<0.05

Due to the thin strut width and other design features, the bare Driver control stent used in these studies often does not provoke a pronounced neointimal proliferative response. Consequently 90 days of neointimal growth was required to permit statistical differentiation of the single Driver and Endeavor responses. In contrast, the additional mechanical burden of overlapped stents amplified the early neointimal response, facilitating separation of the Driver and Endeavor responses at 28 days. In both cases, the inhibitory effect of zotarolimus is lost at later time points due to the robust nature of smooth muscle cell proliferation in the porcine arteries. However, the less intense proliferation of human neointima is anticipated to allow for durable responses.

Pharmacokinetics

The rate of elution of zotarolimus from the implanted Endeavor Zotarolimus-Eluting Coronary Stent System and the distribution of zotarolimus from the stent to surrounding arterial tissues, plasma, and distant organs has been measured using the rabbit iliac artery model (FS97) and the swine coronary artery model (FS114).

Implantation of 12 mm Endeavor Zotarolimus-Eluting Coronary Stent Systems containing 10µg/mm of zotarolimus in either the rabbit iliac artery or the swine coronary artery released over 50% of the drug coating within the first 24 hours after implantation. Stents removed from rabbit iliac arteries at 24 hours after implantation retained on average 43.8% of the initial drug load. Stents removed from swine coronary arteries 24 hours after initial implantation retained on average 34.7% of the initial drug load. By 7 days after implantation, only approximately 2.8% and 5.8% of the initial drug load was retained on stents implanted in rabbit and swine arteries, respectively (Table 4-16).

Table 4-16: Drug Remaining on Explanted Stents (µg/stent; % remaining in parentheses; Studies FS97 and FS114)

	24 hours	2 days	3 days	5 days	7 days	10 days	14 days	28 days
Rabbit (n=6) Study FS97	49.20 ± 6.31 (43.8)	29.25 ± 4.55 (25.6)	18.02 ± 2.83 (16.0)	9.27 ± 3.54 (8.2)	3.32 ± 0.83 (2.9)	–	ND	ND
Swine (n=6) Study FS114	41.67 ± 5.05 (34.7)	39.17 ± 3.76 (32.6)	20.83 ± 6.18 (17.4)	16.33 ± 4.13 (13.6)	7.00 ± 6.42 (5.8)	5.17 ± 1.83 (4.3)	2.17 ± 0.41 (1.8)	0.48 ± 0.26 (0.4)

–, not done; ND, none detected

Blood levels resulting from implantation of the drug-coated stents were generally low and rapidly decreased to levels below the limit of detection. In the rabbit study, blood levels of zotarolimus exhibited a sharp peak at the earliest time point evaluated (0.25 hours) and declined rapidly (Table 4-17). In the swine, much lower peak blood levels were obtained and were observed at a later time after implantation (3 hours). Despite the higher peak blood levels seen in the rabbit, by 7 days after implantation, blood levels were not detectable in either the rabbit or swine.

Table 4-17: Blood Levels of Zotarolimus (ng/mL)

	15 min	1 hr	3 hr	6 hr	24 hr	2 day	3 day	5 day	7 day	10 day	14 day	28 day
Rabbit (n=3-5) Study FS97	177.68 ± 167.07	6.48 ± 1.58	5.26 ± 1.06	3.42 ± 0.77	1.88 ± 0.31	0.99 ± 0.12	0.74 ± 0.11	0.35 ± 0.31	ND	–	ND	ND
Swine (n=3) Study FS114	1.39 ± 0.25	2.36 ± 0.43	2.67 ± 0.67	1.57 ± 0.33	0.68 ± 0.11	0.42 ± 0.05	0.27 ± 0.03	<0.23[1]	ND	ND	ND	ND

[1] Actual value from one swine = 0.23 ng/mL; values from other 2 swine were <0.2 ng/mL; ND, not detected; --, not done

The vessel wall surrounding the stent exhibited much higher drug concentrations than the blood and exhibited sustained levels for longer than drug could be detected in blood. The highest concentration of zotarolimus was observed in the vessel wall surrounding the stent two days after implantation in both the rabbit and swine. This level declined over time, but trace amounts were still detectable 28 days after implantation (Table 4-18). Thus, despite the rapid elution of zotarolimus from the Endeavor stent, the drug was retained within the vessel wall providing for long-lasting pharmacological effects at the intended site of action.

Table 4-18: Drug Present in the Vascular Wall Surrounding the Stent (ng/mg)

	1 day	2 days	3 days	5 days	7 days	10 days	14 days	28 days
Rabbit Study FS97	53.29 ± 36.73 (n=10)	69.07 ± 30.68 (n=6)	36.16 ± 35.22 (n=6)	25.94 ± 33.82 (n=6)	3.92 ± 0.93 (n=6)	--	0.85 ± 0.93 (n=6)	1.38 ± 0.60 (n=6)
Swine Study FS114	23.92 ± 16.95 (n=6)	27.85 ± 9.59 (n=6)	14.61 ± 8.61 (n=6)	14.41 ± 6.97 (n=6)	13.19 ± 7.87 (n=5)	8.85 ± 1.46 (n=6)	4.31 ± 2.82 (n=6)	1.18 ±0.64 (n=5)

Vessel segments distal and proximal to the stent exhibited 2% or less of that found in tissue immediately in contact with the stent.

In the swine, the drug levels in myocardium immediately beneath the stents were also measured. Detectable levels were present for 14 days following implantation, but the levels were somewhat lower than those measured in stented vessels either immediately surrounding the stent or proximal or distal to the stent itself (Table 4-18 and Table 4-19).

Table 4-19: Drug Present in Tissues Near the Stent (ng/mg; Study FS114)

	1 day	2 days	3 days	5 days	7 days	10 days	14 days	28 days
Myocardium	0.34 ± 0.20 (n=6)	0.23 ± 0.08 (n=5)	0.10 ± 0.06 (n=6)	0.06 ± 0.04 (n=4)	0.04 ± 0.02 (n=6)	0.02 ± 0.01 (n=6)	0.01 ± 0.003 (n=4)	ND (n=6)
Proximal vessel	0.42 ± 0.10 (n=6)	0.56 ± 0.29 (n=6)	0.19 ± 0.09 (n=4)	0.30 ± 0.22 (n=4)	0.14 ± 0.11 (n=6)	0.09 ± 0.06 (n=6)	0.06 ± 0.05 (n=6)	0.03 ± 0.02 (n=6)
Distal vessel	0.46 ± 0.23 (n=6)	0.51 ± 0.24 (n=6)	0.27 ± 0.10 (n=6)	0.22 ± 0.09 (n=6)	0.17 ± 0.09 (n=6)	0.39 ± 0.16 (n=6)	0.03 ± 0.02 (n=4)	0.03 ± 0.02 (n=6)

ND, not detected

Distant tissues (lungs, liver, spleen, kidneys, lymph, myocardium, and carotid artery) in the rabbit had levels ≤ 0.05 ng/mg from 24 hours after dosing until measurement was discontinued at 28 days after implantation (Study FS97). Kidney tissue taken from swine had detectable levels of zotarolimus only at 24 hours after dosing, and liver and lung tissue had no detectable zotarolimus present at any time point from 24 hours to 28 days after implantation (Study FS114). Thus, the tissue surrounding the stent received the greatest exposure to the zotarolimus and this exposure persisted long after drug had completely eluted from the stent. Exposure of the rest of the body to zotarolimus from the stent was short lived and very limited in magnitude.

Local Tolerance

The local tolerance and healing of coronary vessels after implantation of the Endeavor stent have been evaluated at various times (i.e., 7, 28, 90, and 180 days) after stent implantation into swine coronary arteries (Studies FS99, FS100, FS101, FS102, FS135) and rabbit iliac arteries (Study FS107). Local tolerance was evaluated by assessing the inflammatory response of the surrounding blood vessel to the stent placement, the degree of medial necrosis or thinning and the amount of vessel injury, and effects on the

myocardium. The healing of coronary vessels was inferred from the degree of endothelialization and the fibrin score.

4.4.2.1 Inflammatory Response

Semi-quantitative histological grading of inflammation yielded scores that were highest at the earliest time point irrespective of treatment group and that decreased to very low levels over time. In the rabbit study (Study FS107), the inflammation scores for both the bare and drug-coated stents decreased substantially between Days 7 and 28. The decrease for the drug-coated stents in the rabbit was slightly less at Day 28 than for the bare stents resulting in a slightly higher inflammation score. In the swine studies (Studies FS99, FS100, FS101, FS102, FS135), both the polymer-coated and drug-coated stents had slightly higher inflammation scores than the bare control stents at multiple time points evaluated after implantation (i.e., 7, 28, 90, and 180 days). Although inflammation scores were statistically significantly higher for coated than the bare stents at up to 90 days after implantation, the inflammation scores for all stents were generally less than 1 after Day 7, indicating a very low level inflammatory response (i.e., involvement of 3 or fewer struts and 10 or fewer inflammatory cells surrounding each strut). By 6 months after implantation, no significant differences were seen between the bare stents and Endeavor stents. Thus, in general, the slightly greater inflammatory response initially seen with the Endeavor stent resolved over time.

As shown in Figure 4-8 below, porcine inflammation scores demonstrated mild response at all chronic time points up to 180 days with single and overlapped stents.

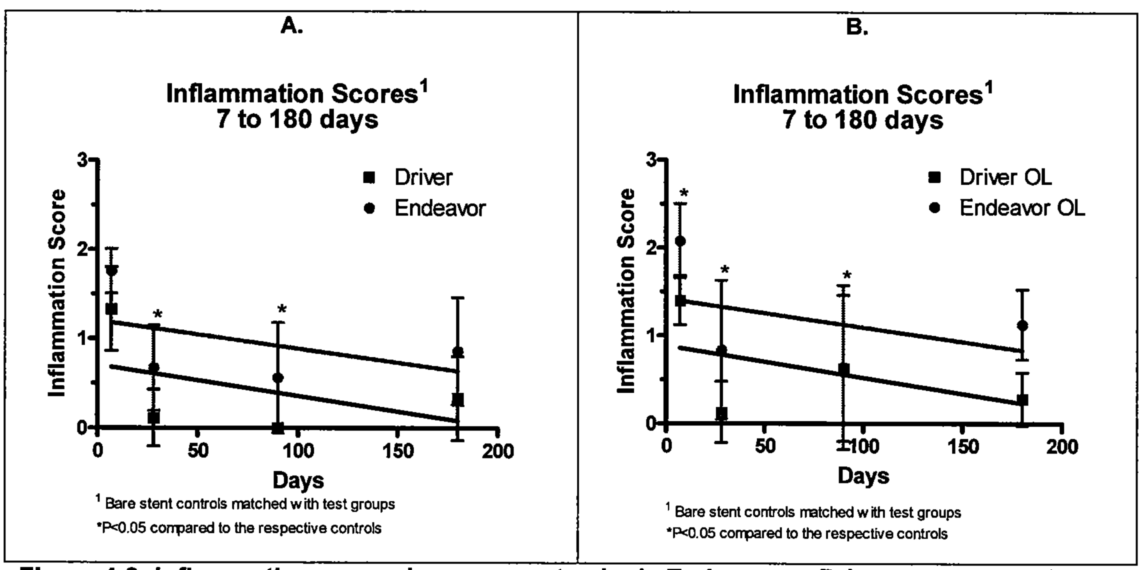


Figure 4-8: Inflammation scores in response to single Endeavor or Driver stents at multiple timepoints up to 180 days (A) indicate Endeavor mean scores of less than one from 28 to 180 days. Inflammation scores in response to overlapped Endeavor and Driver stents (B), show a similar profile to single stents but with slightly higher scores in response to the greater stent burden in the overlapped segment. Lines indicate the trend in inflammation response with time.

Furthermore, as shown in Figure 4-9 below, porcine inflammation scores demonstrated mild response to a 3X or 6X drug over dose at all chronic time points up to 180 days with single and overlapped stents.

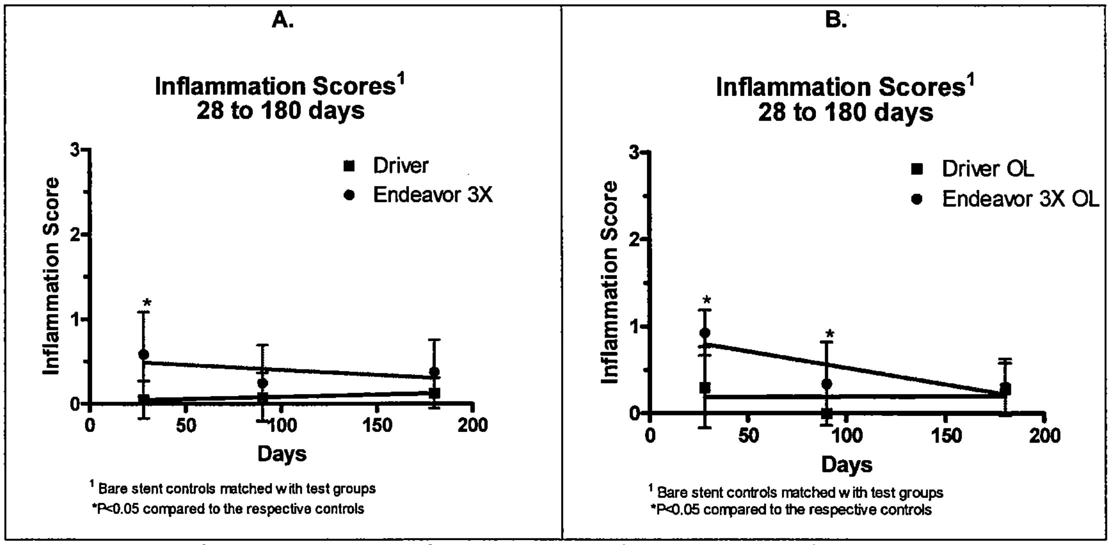


Figure 4-9: Inflammation scores in response to single Endeavor (3x drug load) or Driver stents at multiple timepoints up to 180 days (A) indicate Endeavor (3X drug load) mean scores of less than one from 28 to 180 days which are similar to scores seen with the 1X drug load. Inflammation scores in response to overlapped Endeavor (3X drug load, i.e. 6X drug load in overlap segment) and Driver stents (B), also show a closely similar profile to single stents but without increased scores in response to the greater drug load in the overlapped segment. Lines indicate the trend in inflammation response with time.

In addition, as shown in Figure 4-10 below, porcine inflammation scores demonstrated mild response to PC Polymer at all chronic time points up to 180 days with single stents.